AMENDMENTS TO THE SPECIFICATION:

Please replace the title with the following amended title:

Process for the preparation in pure form of the protease activating blood clotting factor VII, its proenzyme or a mixture of both proteins by means of ~~affinity~~ chromatography.

Please insert the following new paragraph at page 1, line 1:

This is a division of Application No. 09/632,974, filed August 4, 2000 (allowed), claiming benefit to German Application No. 19937218.7, filed August 6, 1999, for which benefit of priority is claimed herein, and both of which are incorporated herein by reference.

Please replace from page 4, line 1, through page 4, line 6, with the following:

The adsorption of the protease on hydrophobic matrices or on hydrophobic ligands which are coupled to appropriate matrices can also be used according to the invention. Examples are phenyl- and octyl-sepharoses ~~octyl-Sepharoses®~~ or a phenylalanine coupled to a matrix. The bound protein is eluted in a manner known per se using a buffered solution of low ionic strength, which can contain phenylalanine, glycerol or ethylene glycol.

Please replace from page 5, line 4, through page 6, line 5, with the following:

In general, however, it is expedient to carry out all process steps for the isolation of the protease and of the corresponding proenzyme from a solution containing these proteins, such as plasma, plasma fractions, tissue fluids or cell culture supernatants of the recombinantly or transgenically expressed protease or mutants thereof in the presence of protein stabilizers. The same also applies to the storage of the proteins

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

mentioned and their use in pharmaceutical preparations. Particularly expediently, a combination of a number of protein stabilizers can be used, where the protein stabilizers should be selected from the following substance groups:

- complexing agents of divalent ions, preferably ~~EDTA, EGTA~~ ethylenediaminetetraacetic acid (EDTA), [ethylenebis(oxyethylenenitrilo)]tetraacetic acid (EGTA), or citrate, and/or
- divalent ions, preferably calcium ions, and/or
- amino acids, preferably glutamate, arginine, lysine or glycine, and/or
- sugars, preferably glucose, arabinose, mannose or mannitol, and/or
- solubilizers, preferably hydroxyproline, and/or
- detergents, preferably ~~Tween® or Triton®~~ a polyoxyethylenesorbitan fatty acid ester (Tween®) or an octylphenoxypolyoxyethanol (Triton®), and/or
- alcohols, preferably ethylene glycol or polyethylene glycol, and/or
- proteins, preferably albumin, gelatin, fibronectin, vitronectin or similar proteins, and/or
- reductants, preferably dithiothreitol, mercaptoethanol or cysteine, and/or
- proteinase inhibitors such as aprotinin, α_2-antiplasmin, C1-esterase inhibitor, the inter-α-trypsin inhibitor, the antithrombin III/heparin inhibitor or synthetic inhibitors.

Please replace from page 6, line 19, through page 6, line 28, with the following:

When using the ~~abovementioned~~ above-mentioned process steps, it is thus possible to obtain both the purified protease activating factor VII, its proenzyme or, alternatively, a mixture of the activated protease and the proenzyme. A route which is

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

particularly worthy of mention for the preparation of a pure activated protease consists in the chromatographic separation of the protease activating factor VII from its proenzyme by means of stepwise elution, in which a substance which has bonds of different strength to the protease on the one hand and to the proenzyme on the other hand is immobilized on the support material. Different eluates can thus be obtained which contain either only the activated protease or only the proenzyme.

Please replace from page 9, line 3, through page 9, line 6, with the following:

Monoclonal antibodies which are directed against the protease activating factor VII were coupled to ~~BrCN-Sepharose®~~ BrCN-sepharose. 30 ml of this mAb matrix were packed into a column and the resin was equilibrated with 50 mM sodium citrate, 0.1 M sodium chloride (NaCl), 0.1 M arginine x HCL, pH 6.0.

Please replace from page 10, line 3, through page 10, line 10, with the following:

A solution containing the proenzyme form of the factor VII-activating protease and which still contained contaminations by other proteins was pumped onto Mono Q ~~Sepharose~~ sepharose in a buffer solution of 20 mM Na acetate, 0.1 M glycine, pH 4.5 and then washed with the abovementioned buffer. The fraction passing through was collected. Bound proteins were eluted using 20 mM Na acetate, 2 M NaCl, pH 4.5. The elute was diluted in a buffer of 5 mM Na citrate, 50 mM NaCl, pH 6.0, and investigated in the test systems mentioned in Example 1. Aliquots were stored at 4 to 8°C or frozen at -20°C.

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com